National Institute on Drug Abuse 2016-2020 Strategic Plan

Executive Summary

[An executive summary will be provided in the final draft]

NIDA's Mission

NIDA is the lead federal agency supporting scientific research on drug use and its consequences. Our mission is to advance science on the causes and consequences of drug use and addiction and to apply that knowledge to improve individual and public health through:

- Strategically supporting and conducting basic and clinical research on drug use, its consequences, and the underlying neurobiological and behavioral mechanisms involved.
- Ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disease.

The strategic priorities outlined in this plan are intended to address the full breadth of complexity related to drug use and its health and social consequences across the spectrum from recreational use to problematic use and *substance use disorders* (SUDs). SUDs include both behavioral and neurobiological components that are strongly influenced by diverse environmental and social factors. Advances in research technologies and informatics are helping us to understand the complex components and underpinnings of SUDs in unprecedented ways. NIDA's strategic priorities for the next five years are designed to leverage these advances to translate our increased understanding of the basic science of the brain and behavior into more effective prevention and treatment interventions that can ultimately reduce the negative impacts of drug use on society. To achieve this mission, NIDA will focus on advancing the following high-level strategic goals:

Introduction

As of 2013, nearly 27 million Americans were current users of illicit drugs and almost 67 million Americans were current users of tobacco products[1]. Drug use and substance use disorders (SUDs) represent major public health problems that affect millions and place enormous burdens on society. The accumulated costs to the individual, the family, and the community are staggering and arise as a

consequence of many direct and indirect effects, including compromised physical and mental health, loss of productivity, reduced quality of life, increased crime and violence, abuse and neglect of children, and healthcare costs. The combined yearly economic impact of these factors is estimated at $193 billion for illicit drug use and $295 billion for tobacco use[2,3].

The profound complexity of human behavior and of behavioral disorders like SUDs requires a deeper understanding of the fundamental processes that give rise to them. How do biological and environmental mechanisms influence behavior and how does the disruption of these mechanisms lead to addiction? A more detailed understanding of the links between genes, brain structure and function, and behavior—in both health and disease—will lead to more personalized and precise interventions to prevent and treat addiction. For example, we now have an unprecedented capacity to screen for thousands of genetic variations and catalogue how they affect addiction risk by influencing brain maturation and architecture, brain-circuit function, and behavioral patterns[4]. NIDA-supported researchers are using whole-genome sequence analysis to identify genes that modulate addiction risk and exploring how environmental factors—such as early life stress and peer influences—can affect the expression of those genes (via epigenetic modifications) to either increase or decrease risk across the lifespan and across different stages of the addiction trajectory.

Stunning technological advances, particularly in the field of neuroscience, are allowing scientists to ask questions that were unimaginable only a few years ago. Ever more powerful tools in neuroimaging, transgenics, opto- and chemo-genetics, molecular modeling, and bioinformatics are supporting the systematic identification of genetic, environmental, and neural circuit variables that influence an individual's risk for drug use and addiction. For example, CRISPER, a powerful new gene-editing technology, is poised to revolutionize biomedical research[5]. This technology is inexpensive, fast and easy to use and has rapidly been adopted by researchers across the country to understand the role of specific genetic variations in complex processes including addiction. This research will identify targets for new therapies that could ultimately revolutionize our prevention, diagnostic, and treatment capabilities.

Recent advances in clinical technologies are also presenting new opportunities for research. Technologies that can target and modulate brain activity, including transcranial magnetic and electrical stimulation and electric deep brain stimulation, as well as neurofeedback techniques, are being explored to translate new knowledge about the underlying neurobiology of addiction into novel diagnostic techniques and personalized therapeutic approaches.

NIDA is also committed to harnessing recent advances in healthcare technologies. Recent federal efforts[6] have led to a rapid increase in the adoption of electronic health records (EHRs) by healthcare providers and spurred advances in other health information technologies, including telehealth and mobile health applications. These technologies have the potential to revolutionize behavioral health care and related research. The synergistic implementation and deployment of these technologies with Big Data mining will allow researchers to draw on unprecedented amounts of health information, transforming our understanding of how individual-level factors contribute to health and disease and

ushering in a new era of personalized medicine. It will also provide a better understanding of how substance use and SUDs influence outcomes for diverse health conditions.

To understand the causes and trajectories of SUDs, it is critical to investigate the biological, medical, social, and economic factors that contribute to them. NIDA strives to translate the returns of its investments in genetics, epigenetics, neuroscience, pharmacotherapy, behavioral science, and health services research into the most effective strategies for preventing and treating substance use and addiction. In addition to advancing basic and clinical sciences related to drug use and its consequences, NIDA prioritizes research efforts relevant to current public health needs, such as:

- The opioid epidemic.
- Changes in state marijuana laws.
- Access to evidence-based SUD treatment.
- Emerging drugs and delivery systems.
- Spread of infectious disease.

The Opioid Epidemic

In recent years, the interrelated epidemics of prescription opioid misuse and heroin use have awakened high levels of public health awareness and concern, demanding a robust, evidence-based, and multifaceted response. An estimated 1.9 million people in the United States suffered from SUDs related to prescription opioid pain medications in 2014, and 586,000 suffered from a heroin use disorder[1]. These high rates of opioid use disorders are accompanied by devastating medical and social consequences including deaths from overdose, a rising incidence of neonatal abstinence syndrome in newborns due to maternal opioid use during pregnancy, and increased spread of infectious diseases such as HIV and hepatitis C (HCV) due to sharing of needles for injection drug use and increased risky sexual behaviors[7–10].

Research has demonstrated the efficacy of multiple types of interventions, including behavioral prevention interventions[11]; monitoring and risk reduction through prescription drug monitoring programs (PDMPs)[12–15]; programs to provide overdose education and distribute the overdose-reversal drug naloxone to opioid users and potential bystanders[8,16,17]; drug courts to increase access to treatment in lieu of incarceration[18]; pharmacological treatments including methadone, buprenorphine, and extended-release naltrexone, combined with behavioral interventions[19–22]; and abuse-deterrent formulations for opioid pain relievers[23,24]. NIDA will continue its close collaborations with other NIH institutes and private industry partners to develop analgesics with reduced abuse potential and to identify biomarkers of pain severity that can be used to evaluate new treatments and further personalized interventions. Similarly NIDA will continue its partnership with other federal agencies and community partners in addressing the challenges posed by abuse of prescription opioids and heroin in this country.

Changes in State Marijuana Laws

Marijuana is the most commonly used illicit drug in the United States, with over 22 million people (8.4 percent) over the age of 11 reporting use in the past month[1]. In light of rapidly-shifting state policies

regarding marijuana use for medical and recreational purposes, it is more important than ever to produce and disseminate accurate information about marijuana's health effects and potential therapeutic uses and to conduct the research needed to fill the gaps in our knowledge.

Regular use of marijuana among adolescents can have detrimental impacts on the developing brain and on social and behavioral outcomes[25]; however it is currently unclear how changes in local, state and national policies will impact – and will be impacted by – adolescent use and related outcomes particularly during the most formative years of learning and development. There are many open questions related to marijuana legalization that research can help to address including how policy changes will affect:

- Use of marijuana and related health outcomes, including its association with mental illness
- Health outcomes—positive and negative—related to "medical" marijuana use
- Usage patterns of other drugs, alcohol, and tobacco
- Public-safety outcomes related to drugged driving, crime, etc.
- Potency and cannabinoid content of commonly consumed strains
- New routes of administration (e.g., vaping, dabbing, edibles)
- Societal norms and perceptions

In addition, more research is needed to develop prevention interventions that target marijuana use among youth in the context of changing norms, to understand the health consequences related to the increasing potency of marijuana, and to develop new treatment strategies for cannabis use disorders. NIDA-supported science aims to address these gaps and to help inform decision making related to state and federal marijuana policies. In addition, in line with NIDA's mission of reducing the burden of drug use and SUDs, ongoing research will continue to explore the therapeutic potential of marijuana-derived compounds for pain and addiction.

Implementation of Evidence-Based SUD Treatment

Addiction is a complex but treatable disease that affects brain function and behavior. Unfortunately, we have a significant and ongoing treatment gap in our Nation. Among those who need treatment for a SUD, few receive it. In 2014, 22.5 million Americans needed treatment for a substance use disorder, but less than 12% received treatment at a specialty substance abuse facility[1]. Further, many specialty treatment programs do not provide current evidence based treatments – less than fifty percent provide access to medication assisted treatment for opioid use disorders[26]. NIDA is committed to reducing this gap using a multipronged approach including health services and implementation research to:

- Sustainably implement evidence-based treatments for SUDs in diverse healthcare settings including primary care and the criminal justice system
- Identify strategies to increase access to evidence based treatments including pharmacotherapies for SUDs
- Develop strategies for identifying individuals with problematic drug use and link them with appropriate care

- Identify strategies for addressing stigma and discrimination to encourage people to seek treatment

In addition, NIDA works with diverse stakeholders to raise awareness among both healthcare professionals and patients about the value of addiction treatment and to encourage patients with problematic drug use to seek care. Our NIDAMED and Blending Initiatives develop medical education courses and materials to train clinicians on evidence-based practices related to prescribing for pain, on how to identify individuals with risky substance use, and on how to treat adolescents with SUDs. In addition, NIDA, through the NIH Pain Consortium, helps to fund 12 Centers for Excellence for Pain Education (CoEPEs) that act as hubs for the development, evaluation and distribution of pain management curriculum resources for medical, dental, nursing and pharmacy schools.

Emerging Drugs and Delivery Systems

NIDA monitors and investigates emerging threats to public health stemming from new patterns of drug use. One current trend of concern is the increasing use of synthetic drugs, including synthetic cannabinoids (e.g., K2, herbal incense), synthetic cathinones (e.g., bath salts, "flakka"), and synthetic hallucinogens (e.g., 2-C, NBOME). Recent surges in calls to poison control centers, hospitalizations, and deaths linked to consumption of synthetic drugs have prompted concern across the country[27]. Research is needed to better understand the pharmacology and health effects of these synthetic drugs, socio-cultural factors that influence use, and effective strategies for prevention and treatment.

Another trend that NIDA researchers are watching closely is the rising popularity of e-cigarettes and vaporizer (vape) pens. E-cigarettes are often promoted as safer alternatives to traditional cigarettes, which deliver nicotine by burning tobacco, but little is actually known about the health risks of using these devices. While they do not produce tobacco smoke, e-cigarettes still contain nicotine—a highly addictive drug—along with other potentially harmful chemicals and additives, such as formaldehyde, acetaldehyde, and toxic metals[28]. E-cigarettes are increasingly popular among adolescents, a population that is particularly vulnerable to the addictive power of nicotine and other drugs; a recent study found that adolescent e-cigarette users are significantly more likely to begin smoking conventional cigarettes compared to those who have not used e-cigarettes[29]. NIDA is also concerned about the use of these devices for administration of other drugs, including high potency cannabis extracts (hash oil) and synthetic cannabinoids. It is not yet clear how these devices will affect risk for addiction or other adverse health effects.

Spread of Infectious Disease

Between January and August 2015, a rural community of 4,200 residents in southern Indiana saw the emergence of 181 new HIV cases[30], mostly linked to the injection of the opioid medication oxymorphone[7]. This highlights that injection drug users (IDUs) cannot be ignored in the goal to achieve an AIDS-free generation. Even in the United States, where significant progress had been made in reducing the number of new HIV infections attributable to IDU[31], the latest report coming out of Indiana highlights the challenges that IDU presents to tackling the HIV epidemic. Effective, evidence-based strategies exist for preventing the spread of HIV and other infectious diseases among drug using populations. These include the use of antiretroviral therapy as prevention for HIV transmission--a

strategy known as seek test treat and retain (STTR)[32]--combined with treatment for opioid use disorders with medication assisted treatment to improve compliance with antiretroviral treatment[33]. However, implementation of these treatment strategies among substance users has been slow, highlighting the need for new research on strategies to scale up efforts in this area.

Cross-Cutting Themes

Throughout the strategic planning process, a number of cross cutting themes emerged that are relevant across multiple goals and objectives. NIDA will work to ensure that these themes are addressed across institute programs and initiatives. These cross-cutting elements include:

- Advancing basic research on neuroscience and biology
- Leveraging technology
- Driving innovation
- Collaboration
- Data and resource sharing (data harmonization)
- Supporting health equality
- Increasing the real-world relevance of research (translation)

Advancing basic research on neuroscience and biology

Advancing fundamental knowledge of basic biological and especially neurobiological processes is critical for advancing our understanding of the effects of drugs and in guiding the design of interventions to prevent and treat SUDs.

Leveraging technology

The last few years have seen tremendous advances in the development and implementation of technologies that have great promise for accelerating research on drug use and addiction. Particularly prominent are technologies for gene sequencing, epigenetic analyses, neuronal cell classification, brain imaging, and modulation of brain circuits. Also relevant is the expanding access to increasingly larger databases of genetics, epigenetics, transcriptomics, and clinical health data – through electronic health records and mobile health technologies – along with rapid progression of analytics, computational and information technologies. Programs such as the BRAIN Initiative, the NIH Blueprint, and the NIH Common Fund are helping to drive accelerated technology development. NIDA will actively follow these advances and look for opportunities to capitalize on these developments to advance research on drug use and addiction.

Driving innovation

The biomedical research workforce in this country includes a tremendous number of talented and dedicated scientists with innovative ideas for how to advance research. NIDA will work to encourage and reward innovation to drive advances in addiction research by (1) promoting interdisciplinary collaborations, (2) encouraging research and development through our small business innovation research (SBIR) program, (3) crowdsourcing the development of novel technologies and solutions through challenge grants, (4) supporting innovative researchers through novel mechanisms including our Avenir Awards Program, and (5) supporting training in cutting edge areas important for driving innovation (e.g. data science).

Increasing Scientific Rigor and Reproducibility

Reliable and reproducible research findings are essential to the advancement of science. Over the last few years, multiple studies have reported a troubling lack of reproducibility of biomedical research

findings[34–36]. Though part of this lack of reproducibility could reflect biological diversity other factors that are likely to contribute to it include: selective reporting of data, invalid statistical methods, insufficient transparency in reporting key methodologies and findings, and a failure to train students in ethical scientific practices. NIDA is committed to the responsible stewardship of public funds and will focus on enhancing the reliability of the research. To this end, NIDA will actively contribute to the NIH-wide Rigor and Reproducibility Initiative, participate in relevant activities of scientific organizations focused on enhancing reproducibility through education and outreach, and make concentrated efforts to improve both the quality and credibility of addiction research.

Promoting Collaboration

Fulfilling NIDA's mission will require effective partnerships with and between stakeholders throughout the community, including collaborations between scientists, healthcare providers, engineers, informaticists, healthcare payers, pharmaceutical and biotechnology companies, public health organizations, patients and families, people in recovery, community prevention organizations, educators, federal and state agencies, and others. NIDA will facilitate collaboration among researchers in disparate fields and between researchers and the community. In addition, NIDA will work to maximize the impact of our research by working directly with diverse stakeholders to improve dissemination of NIDA research, support more rapid uptake of evidence-based practices, facilitate critical connections between areas of research, improve translation of basic findings to clinical interventions, and drive evidence-based decision making across the community.

Encouraging Data and resource sharing (data harmonization)

Data sharing is an essential element of applying the power of data science and information technology (Big Data) for SUD research. Harnessing large quantities of data generated by researchers across the world has numerous methodological and economic advantages and provides tremendous opportunities for gaining new insight into addiction. To realize this benefit, however, there are many challenges to be overcome. In particular, scientists and users from diverse areas need to be able to find data easily and to analyze them in new ways. Combining data from various sources and formats requires implementation of data standards as much as possible, which can be achieved via usage of common data elements, shared ontologies, and data dictionaries. Operational challenges related to data curation, development of advanced analysis tools (including machine learning and artificial intelligence techniques) and visualization strategies, and establishment of a culture of data sharing and open access within the scientific community, need to be addressed. NIDA will work to develop practices and approaches that create incentives for sharing data and for secondary analysis of existing data sets.

Supporting health equality

NIDA is committed to addressing health disparities, studying unique SUD issues of underrepresented populations, and supporting health equality research across the life span. This requires considering the impact of age, sex, gender, race, ethnicity, culture, and socioeconomic status on substance use and SUDs. NIDA will work to ensure that these factors are adequately addressed in the research we support.

Increasing the real-world relevance of research

NIDA is committed to making our sponsored research more relevant and applicable to real-world settings by proactively tackling relatively neglected and challenging issues such as poly-drug use (which will require the development of validated animal models), non-treatment-seeking populations, and patients with complexities (e.g., elderly, incarcerated, pregnant, military, and patients with multiple psychiatric and medical comorbidities).

Strategically supporting and conducting basic, clinical, and translational research on drug use, its consequences, and the underlying neurobiological and behavioral mechanisms involved

The central focus of NIDA's mission is to support and conduct biomedical research to understand, prevent, and treat drug use and its consequences. The goals and objectives laid out in this strategic plan provide an overview of the broad research priorities in this area spanning basic science, translational, clinical, applied, and population based research. In addition, this plan outlines five priority focus areas that present unique opportunities to leverage over the next five years.

The four strategic goals are:

- GOAL 1: Identify the biological, environmental, behavioral and social causes and consequences of drug use and addiction across the lifespan
- GOAL 2: Develop new and improved strategies to prevent drug use and its consequences
- GOAL 3: Develop new and improved treatments to help people with substance use disorders achieve and maintain a meaningful and sustained recovery
- GOAL 4: Increase the public health impact of NIDA research and programs

In addition, this plan outlines five priority focus areas that present unique opportunities to leverage over the next five years.

1. Understanding the complex interactions of factors influencing drug use trajectories
2. Accelerating development of treatments
3. Addressing real world complexities
4. Advancing bi-directional translation
5. Building a strong, diverse, multi-disciplinary scientific workforce

Goals and Objectives

GOAL 1: Identify the biological, environmental, behavioral, and social causes and consequences of drug use and addiction across the lifespan

The human brain is incredibly complex, with hundreds of billions of neurons and glial cells interacting to enable us to think, feel, perceive, learn, and act in extraordinarily nuanced ways. Recent advances in neuroimaging, opto- and chemo- genetics, genetics, epigenetics, and other research technologies are revolutionizing our understanding of the brain and brain disorders, spanning molecules, cells, circuits, systems, and individual and social behaviors, in ways not possible even a decade ago.

This goal includes a focus on basic science, which involves investigating fundamental brain functions relevant to drug use and addiction, such as reward, motivation, decision making, impulse control, emotional regulation and stress reactivity, among others. Fully understanding a circuit requires identifying and characterizing the component cells, defining their synaptic connections, observing the dynamic patterns of activity as the circuit functions in the living brain, and perturbing these patterns to test their significance. It also requires an understanding of the algorithms that govern information processing within a circuit and between interacting circuits. Basic studies of neuronal, glial, and neural circuit functions and how they are perturbed by drugs is also fundamental for identifying new therapeutic targets, feeding the translational pipeline toward development of new prevention and treatment strategies.

The President's BRAIN Initiative is accelerating technology development in neuroimaging and brain-circuit manipulation, driving a qualitative shift in the questions we can answer through research. Much of the research conducted under this initiative in the past few years has focused on a few isolated brain regions but these new tools and maps are beginning to provide us with the opportunity to study the complex interactions that exist among neurons and functional brain circuits and how these are influenced by genetics, environment, drugs and addiction and how they respond to treatments. This fundamental knowledge will allow researchers to start to address critical public health questions such as:

- How, when, and for how long to intervene (for both prevention and treatment)
- How to maximize prevention of SUDs
- How to enhance treatment response and recovery
- How to mitigate harms

Advances in genetic and epigenetic approaches are contributing to our understanding of the causes of drug use, abuse, and dependence. We now know that SUDs are complex developmental disorders with high heritability that are also strongly influenced by environment—particularly, during childhood and early adolescence[37]. New genetic methodologies are needed to elucidate the complex interplay of genetic and environmental factors across developmental trajectories of SUDs and comorbid conditions.

Gene-discovery efforts provide the foundation for identification of drug targets, tailoring treatments by genotype (pharmacogenetics) and ultimately defining how environmental factors interact with genetic factors to contribute to SUD risk. By comparing SUD gene-discovery data sets with other genome-wide

association studies (GWAS), it is possible to identify gene variants that are co-morbid with other disorders. Human genetic data will be used to inform preclinical genetic studies and vice versa, so that animal genetic studies can advance our understanding of human addiction.

Recent advances in genome editing using techniques such as CRISPR/Cas9[5] provide the necessary tools to study reward phenotypes through precise manipulation of gene expression within specific neuronal populations. Studies using cell culture models of human neurons from people suffering from SUDs are allowing researchers to understand the effects of drugs on human neurons in vitro—which can be used to validate animal models. In addition, the arsenal of tools to directly modify the activation of brain cells (optogenetics, Designer Receptors Exclusively Activated by Designer Drugs [DREADDS]) is allowing causal investigation of circuits and behavior in animals and the effects of drugs of abuse[38,39].

To improve our understanding of the range of factors that mediate drug use behaviors and risk for addiction and build the foundation for future interventions, NIDA will support the following objectives:

- Characterize the genetic, neurobiological, environmental, and developmental factors that mediate risk and resilience for drug use and addiction
- Identify the factors that influence drug use trajectories
- Establish the effects of drug use, addiction, and recovery on genes, molecules, cells, brain circuits, and health across the lifespan
- Identify the bi-directional effects of drug use and common comorbidities

Objective 1.1: Characterize the genetic, neurobiological, environmental, social and developmental factors that mediate risk and resilience for drug use and addiction

Like most behavioral health disorders, SUDs are polygenic disorders with a complex pattern of inheritance that results from the combined effects of multiple genes and their interaction with the environment[37]. There are likely to be many regions of the genome that contribute to SUD risk, and their individual effects may vary across developmental stages. Understanding the confluence of biological, behavioral, environmental, social, and developmental factors that mediate risk and resilience will provide a foundation of knowledge necessary for designing new prevention and treatment strategies that are tailored towards an individual's unique risk profile.

Understanding the gene x development x environment (GxExD) interactions that contribute to the risk for SUD phenotypes using GWAS will require methods to overcome statistical challenges due to multiple comparisons. One of the primary challenges to understanding how these factors contribute to the various stages of SUDs (e.g., escalation, relapse, etc.) is to determine how to detect relatively small genetic effects that contribute to the overall heritability of SUDs and then examine how these genetic effects operate within changing environments and across human development. Though GWAS has been one of the most productive methods for identifying genetic variants associated with disease, the reduced costs and high throughput of genome sequencing will make it increasingly feasible to apply it for SUD research. The development of advanced analytical and computational tools will be essential to take advantage of this rich information.

In addition, mice with defined genetic backgrounds (e.g., inbred strains, recombinant inbred strains, strains carrying defined naturally and induced genetic variations, etc.) provide a way to test gene x environment, and gene x development interactions under controlled experimental conditions.

Approaches

- Conduct human molecular genetics studies, including large-sample GWAS and genome sequencing, to identify genetic variants that contribute or provide resilience to SUDs.
- Integrate GWAS and sequencing efforts with phenotype identification, environmental effects, postmortem molecular changes, and epigenomic characterization across human development.
- Expand efforts to characterize epigenetic modifications associated with SUDs.
- Functionally validate and characterize SUD-related gene variants in animal models and identify opportunities for clinical translation.

Objective 1.2: Identify the factors that influence drug use trajectories

SUDs are complex conditions that develop over time and are characterized by stages of initiation, escalation, problematic use, and addiction, the latter often being associated with cycles of withdrawal and relapse. However, not all individuals who initiate drug use progress to addiction; some discontinue use quickly, and others maintain a low level of use without escalating to problematic use or addiction. Also, some individuals who develop problem use or addiction are able to stop without formal treatment, whereas others are treatment resistant[40,41].

Genetic epidemiology suggests that individual trajectories are influenced by the environment, the age of initiation, and genetic vulnerabilities. Initiation and dependence share some common genetic factors, but unique genetic factors also underlie the different stages of substance use, as well as individual vulnerability for addiction to particular substances[42].

The heterogeneity of substance use phenotypes and individual genetic variation present significant challenges for understanding the genetic and environmental factors that mediate the development of SUDs. Identifying and characterizing biologically relevant phenotypes will enhance the probability of identifying risk genes, relevant environmental and social risk and protective factors, development factors associated with SUD behavior, and, ultimately, objective diagnostic biomarkers.

Approaches

- Conduct longitudinal studies to examine the impact of drug use on development (see ABCD study highlight).
- Improve standardization and depth of phenotypic and environmental characterization.
- Support efforts to develop large data sets, integrating data across many scientific disciplines and data types to support more complete characterization across stages of the SUD trajectory.

Objective 1.3: Establish the effects of drug use, addiction, and recovery on genes, molecules, cells, brain circuits, and health across the lifespan

Drug use has a broad range of direct and indirect consequences. The direct physiological effects on the user depend on the specific drug(s) used, dose, method of administration, and other factors. Acute effects can range from subtle molecular changes to overdose and death. While the major acute effects are known for many drugs, basic research is still necessary to understand the potential dangers of emerging drugs such as synthetic cannabinoids (e.g., K2, herbal incense) and synthetic cathinones (e.g., bath salts).

Chronic drug use can also have distinct effects on physical and mental health. Researchers are just beginning to understand the effects of chronic drug abuse on, for example, epigenetics, brain energetics, synaptic plasticity, and less studied cell types such as glia that act to support neurons. All of these effects may vary across the trajectory of drug use and addiction. Drug use also has diverse indirect effects such as affecting a user's nutrition and sleep[43,44]; decision making and impulsivity[45]; risk for trauma, violence, injury, and communicable diseases[7,9,46–49]; and outcomes such as educational attainment, employment, housing, relationships, and criminal justice involvement[50–54]. These consequences can all contribute to the trajectory of addiction and may need to be considered independently and collectively when developing treatment interventions.

Approaches

- Explore the epigenetic consequences of drug use, addiction, and recovery.
- Use established or novel behavioral models of each stage of addiction to more completely characterize effects on genes, molecules, cells, circuits, and overall health across the lifespan.
- Investigate the causal role of changes to brain-circuit function in addiction using advanced transgenic technologies (such as optogenetics and DREADDs) to target cell types.
- Utilize advanced technologies (such as multi-electrode arrays, multi-angle cameras, mobile sensing and analytics tools) to investigate complex brain circuits, networks, and behaviors linked to drug use and addiction.

Objective 1.4: Identify the bi-directional effects of drug use and common comorbidities

Addiction frequently co-occurs with other psychiatric conditions, viral infections, and pain disorders[7,9,55,56]. The relationships between these comorbidities confer unique treatment needs on the respective patient populations. Comorbidities may also point to shared biological substrates, environmental influences, and social conditions that give rise to SUDs and these comorbidities. Full characterization of the interactions between these disorders will drive the development of improved treatment strategies for patients with complex SUD phenotypes.

Approaches

- Identify bidirectional risk factors for, and impact of, co-occurring psychiatric and physical health conditions (e.g., HIV, HCV, pain, depression, insomnia) on addiction.
- Evaluate the effectiveness of treatments for general health comorbidities—including the newly approved HCV antiviral—in individuals with problematic drug use and SUDs.

- Identify the molecular, cellular, behavioral, and neurobiological interactions between pain and addiction.
- Characterize the bi-directional effects of common comorbidities and recovery from SUDs.

GOAL 2: Develop improved strategies to prevent drug use and its consequences

Considerable evidence has accumulated over the past four decades that substance use problems can often be prevented through interventions targeting one or more risk or protective factors. Interventions targeting child and adolescent risk factors for drug abuse may reduce other behavioral health problems as well, such as aggression, and improve educational and later life outcomes. Some interventions have been found to show continued effects long after intervention exposure, and many deliver a significant return on investment in terms of reduced societal costs[11,57,58].

Genetics have been shown to account for roughly half of the risk for SUDs[42]. Environmental influences include social as well as biological factors arising from prenatal and childhood environments that influence both gene expression (epigenetics) and development—such as stress, nutrition, parental drug use, or illnesses (including pain) that affect an individual's likelihood to use drugs[52,59–61]. Socio-cultural environments (e.g., policy, peers, family, and communities) also play pivotal roles in the initiation of drug use, escalation of use, and SUD trajectories[52,62].

An increased understanding of neurodevelopmental adaptations to the environment that influence risk of substance use is leading researchers to think of prevention as affecting not only behavior but also brain development and function, including neuroendocrine stress responses and neuroplasticity. For example, maltreated children receiving a prevention intervention for preschoolers in foster care not only showed improved behavioral functioning (leading to increased likelihood of successful transition into permanent homes) but also showed better stress regulation (measured by cortisol levels), approaching that of a control group of children in the general population[63,64]. Thus we are entering the era when neurodevelopment can be directly targeted and assessed through prevention science.

Most substance use begins during adolescence, and aspects of brain development, such as the slow maturation of the frontal cortex, interact synergistically with social pressures arising from new social roles, peer environments, and stressful life transitions to heighten risk during this period[65]. In addition patterns of behavior and interaction in family, school, and peer contexts become more established as the child moves into adolescence; consequently, while prevention interventions aimed at older children and teenagers can be effective, they have a greater challenge in positively influencing the decisions of youth who may for various reasons be on a risky life track.

Vulnerability for substance use and related problems has been shown to peak during critical life transitions—including biological transitions such as puberty and social/environmental transitions such as attending a new school, parental divorce or military deployment, or graduation[59,66–69]. Despite strong evidence supporting the effectiveness of prevention, relatively few effective interventions have been widely adopted or faithfully implemented, and thus their potential to positively impact public health has been limited[70]. Implementation research is thus an important part of this overall prevention goal, as is capitalizing on the opportunities generated by healthcare reform. Unprecedented and rapid change in healthcare policy and technology has the potential to expand not only the reach of treatment but also to improve the delivery of evidence-based prevention interventions.

To design and deliver targeted prevention approaches to the individuals and communities who stand most to benefit from them, NIDA will support prevention research that builds on our growing experience evaluating prevention interventions and that leverages the accumulating basic science on the developmental, biological, genetic, and neurobiological mechanisms underlying drug use and addiction. To facilitate the development of new prevention strategies, NIDA will support research to:

- Determine the mechanisms that underlie individual risk for addiction and common comorbidities.
- Develop and test innovative prevention interventions that target mechanisms underlying risk factors.
- Develop and test strategies for effectively and sustainably implementing evidence-based prevention interventions.

Objective 2.1: Determine the mechanisms that underlie individual risk for addiction and common comorbidities

To inform the development and implementation of effective prevention interventions for SUDs, it is important to better understand the mechanisms through which interventions work and for whom they are most effective. Determining the mechanistic effects of effective programs and interventions will provide an evidence base to guide efforts to refine and improve program components. Building this evidence base will require research on the individual predictors of intervention success and on the malleable mediators of intervention effects, as well as research to clarify which preventive components best predict intervention-related outcomes and for whom. Further research is needed to refine our understanding of modifiable risk and protective factors associated with life transitions and developmental periods to enhance the power of interventions. In addition, a greater understanding of the impact of preventive interventions on neurobiology is needed in order to identify the critical windows across the lifespan during which interventions may produce the greatest impact for specific populations.

This goal will build upon basic research to help determine the types of interventions that are most likely to be effective for specific individuals or subpopulations given underlying biological mechanisms of action.

Approaches

- Establish the mechanisms through which preventive interventions effectively influence the biological, behavioral, and social mediators of risk for substance use disorders.
- Identify mediators of the effectiveness of prevention interventions for different populations and developmental stages.
- Explore the common underlying mechanisms that lead to multiple problem behaviors including substance abuse.

Objective 2.2: Develop and test innovative prevention interventions that target mechanisms underlying risk factors

Changes in technology and the social media landscape are presenting new opportunities to deliver innovative prevention interventions. In addition, the accumulating basic science of biological, environmental, and developmental interactions underlying substance use and addiction, combined with our increasing understanding of the mechanisms underlying behavior change and intervention effectiveness, will allow researchers to develop and test prevention interventions targeted to the mechanisms underlying risk and resilience for drug use and related disorders. For example, child maltreatment is one of the most powerful environmental risk factors for SUDs and other behavioral disorders[71]. The development of interventions that identify and address the consequences of child abuse and neglect may offer effective prevention for a large population of vulnerable individuals. This goal includes integrating discoveries from the basic biological, behavioral, and social sciences to develop and test innovative preventive interventions that specifically target underlying mechanisms in drug abuse risk.

Priorities within this goal include development and testing of prevention interventions for known high-risk and vulnerable populations and for subgroups for which research gaps exist (e.g., seniors), and to develop interventions to address emerging drug trends and drug-use practices (e.g., e-cigarettes, synthetic drugs, "dabbing") that have unique characteristics or confer unique risks. Novel intervention approaches, adaptive designs, and other methods for optimizing interventions are also needed.

Approaches

- Integrate discoveries from the basic biological, behavioral and social sciences to develop and test innovative preventive interventions that specifically target the underlying mechanisms of drug abuse risk and other related problem behaviors.
- Build on developmental research to maximize the effectiveness of interventions at different critical developmental stages and transitions from infancy to adulthood.
- Explore the potential of technology-based methods for delivering prevention interventions, such as smartphones, video games, and social media.
- Develop and test effective preventive interventions targeted to factors underlying common comorbidities including mental illness, behavioral problems, pain, etc.
- Develop and test preventive interventions for implementation in diverse clinical settings including emergency departments, primary care offices, hospital inpatient settings, high school and college health centers, etc.

Objective 2.3: Develop and test strategies for effectively and sustainably implementing evidence-based prevention interventions

To increase the public health impact of effective prevention interventions, increased attention must be given to two types of implementation science: research that considers implementation and scale-up issues during intervention development and testing in order to increase the likelihood of uptake; and research to develop and test systematic, measurable, and replicable strategies for optimizing the adoption, uptake, and sustainability of evidence-based prevention interventions and practices with fidelity in real-world settings. NIDA will support research on the complex processes through which

evidence-based interventions are adopted, implemented, and sustained at the community level, with a strong orientation toward devising empirically-driven strategies for increasing their population impact.

Research is needed to test novel modes of intervention delivery, as well as to understand factors that influence the integration and sustainability of evidence-based prevention interventions across community and healthcare settings. This goal will also prioritize the development of new quantitative methods for data analysis and experimental design, as well as benefit-cost analyses to facilitate uptake and support for investing in prevention by policymakers and funders.

Approaches

- Identify obstacles to large-scale implementation of evidence-based preventive interventions and develop approaches to resolving those obstacles.
- Identify the infrastructure and training needed to support large-scale adoption, implementation, and sustainability of evidence-based preventive interventions.
- Identify ways the Affordable Care Act and related regulatory changes can best be leveraged to increase implementation of prevention interventions for substance use and related problems.
- Explore the use of technology to improve the dissemination and sustainable implementation of evidence-based prevention interventions.

GOAL 3: Develop new and improved treatments to help people with substance use disorders achieve and maintain a meaningful and sustained recovery

The last few decades have seen dramatic advances in our understanding of the biology of addiction, but the range of treatment options available for most SUDs remains limited. FDA-approved pharmacotherapies exist for dependence on opioids (i.e., methadone, buprenorphine, and extended release naltrexone), alcohol, and nicotine, and psychosocial treatments (e.g., cognitive behavioral therapy, contingency management, etc.) are available for other SUDs[72,73], but the efficacy of these treatments is far from ideal. There is a clear need to develop better treatment strategies that target the biological substrates of addiction across stages – including detoxification, maintenance, and relapse prevention.

SUDs are chronic conditions that often require long-term management. The chronic nature of the disease means that relapsing to drug abuse is common, with recurrence rates similar to those for other well-characterized chronic medical illnesses that have both physiological and behavioral components—such as diabetes, hypertension, and asthma[74]. SUDs can be managed successfully in many cases, but available treatments are ineffective for others. In addition, the vast majority of individuals who have SUDs never seek treatment[1].

There are many new approaches that show promise for the treatment of SUDs in preclinical studies including novel pharmacotherapies, behavioral therapies, vaccines, biofeedback, and direct manipulation of brain activity via transcranial magnetic stimulation and electrical deep brain stimulation[75–79]. Translating these promising interventions into clinical practice will require testing their efficacy in target populations in clinical trials. However, a key challenge in this area is the reticence of

pharmaceutical companies to develop treatments for addiction. This is due in part to the perception that the market for such treatments is small and to difficulties conducting clinical trials in patients with multiple comorbidities. In addition, the only end point currently accepted by the FDA for clinical trials examining therapeutics for substance use disorders is abstinence. This represents an unrealistically high bar, which discourages investment by the private sector[80]. NIDA, together with the FDA and our academic and industrial partners, is working towards establishing end points other than abstinence, and this will remain a strategic priority over the next five years.

The ongoing transformation of the healthcare system also presents significant opportunities for advancing treatment for SUDs. Health reform initiatives are promoting the integration of behavioral health care into general health services. In addition, new payment models—including shared savings programs and the hospital readmission penalty—are creating financial incentives for addressing broader issues that contribute to treatment success and long-term outcomes, including SUDs. Medical costs for treating patients with chronic physical health conditions can be two to three times higher in patients with comorbid behavioral health disorders[81], and untreated SUDs are associated with poorer adherence to treatment plans and medications, leading to worse outcomes[82]. However, less than 12 percent of people with SUDs receive treatment, and only a fraction of those receive care that is adequate, making addressing SUDs a prime target for reducing healthcare costs[1]. Research can help to define how best to identify individuals with problematic substance use or SUDs in general healthcare settings and engage them in appropriate treatment.

Another element of the changing healthcare landscape that has the power to affect SUD treatment is the rapid development and adoption of technologies including electronic health records, telehealth, and mobile health technologies. These technologies have the power to revolutionize health services research and to drive new treatment delivery models by supporting more effective integration of care, extending the reach of the SUD treatment workforce, enabling real-time patient monitoring and support, delivering technology-based intervention, and engaging patients who are hesitant to participate in the traditional behavioral health treatment system. Research is needed to inform how best to leverage these new technologies to improve patient outcomes.

The ultimate goal of NIDA research is the amelioration of the disease burden caused by addiction; the development of effective interventions is vital to the realization of this goal. To facilitate the development of innovative intervention strategies, NIDA will support research to:

- Develop and test novel treatments based on the science of addiction
- Develop and test metrics for measuring the quality and efficacy of treatment
- Identify biomarkers that predict response to treatment and risk for relapse
- Develop and test strategies for effectively and sustainably implementing evidence based treatments

Objective 3.1: Develop and test novel treatments based on the science of addiction

Recent advances in our understanding of the genetic, epigenetic, and neurobiological mediators of addiction have led to the identification of a range of potential therapeutic targets. New interventions are particularly needed for SUDs for which there are currently no FDA-approved medications, such as cocaine, methamphetamine, and cannabis use disorders[72]. In addition, developing new and improved treatment options for opioid use disorders remains a high priority due to the scope of the current opioid epidemic[83]. NIDA will focus on supporting a robust translational pipeline of compounds, biologics, and non-pharmacological interventions (e.g. transcranial magnetic stimulation, behavioral interventions) to be developed as potential treatments for SUDs.

The President's new Precision Medicine Initiative aims to develop the research infrastructure to begin to delineate individual biological factors that contribute to treatment outcomes. This initiative will set the groundwork for developing treatment strategies based on a person's unique DNA profile to achieve the greatest health benefit with fewer side effects (pharmacogenomics). Research has identified genetic variations that influence response to drugs as well as risk for substance use disorders, including genes for enzymes that metabolize drugs, neurotransmitter receptors and transporters, and enzymes that mediate neurotransmitter synthesis or degradation[42,84,85]. Understanding how genetic variations contribute to response to treatment will advance the development of more therapeutic interventions.

Approaches

- Integrate discoveries from basic science to develop and test new chemical compounds and innovative behavioral treatment interventions that specifically target the underlying neurobiological mechanisms of SUDs.
- Develop and test new non-pharmacological approaches to treat SUDs.
- Expand testing of pharmacogenomic approaches for treating SUDs.
- Explore how healthcare technologies can be used to improve patient diagnosis and personalize treatment.

Objective 3.2: Develop and test metrics for measuring the quality and efficacy of treatment

One of the principles of current health reform efforts is that health care may be improved through the development and use of clinical quality measures. New healthcare payment and delivery models that create financial incentives based on quality performance measures are emerging. Efforts are underway to incorporate these types of measures into a "learning healthcare system" that continuously monitors performance and strives to rapidly adjust practices to improve outcomes.

In 2006, the Institute of Medicine recommended developing and implementing a quality measurement and reporting infrastructure as part of an overall strategy for enhancing the care provided in the field of SUD treatment[86]. The creation of valid and reliable quality measures that can be monitored and acted upon to drive improvements in identification and treatment of people with SUDs is a critical mechanism through which the behavioral health field can contribute to the ongoing evolution of the healthcare system.

Currently, almost all clinical quality measures used to evaluate addiction treatment are process measures that evaluate the services provided—for example, whether or not a patient was counseled about the mediations available for opioid use disorder treatment. There is a significant need to develop and test outcome measures that evaluate patient response to treatment.

In addition to use in the healthcare system, valid outcome measures that can serve as end-point measures for clinical trials of therapeutics for SUDs are also urgently needed[87]. Over the next five years, NIDA will prioritize the development of metrics that measure the quality and efficacy of addiction treatments, leveraging existing measurement standards–such as the NIH Patient Reported Outcomes Measurement Information System (PROMIS)–when possible.

Approaches

- Identify target metrics that are effective indicators of long-term treatment efficacy.
- Develop and test new end-point measures (other than abstinence) for clinical trials of SUD therapeutics.
- Develop clinical quality measures for implementation in diverse healthcare settings.
- Determine the influence of health care provider training and experience on patient outcomes.

Objective 3.3: Identify biomarkers that predict response to treatment and risk for relapse

An impediment to understanding addiction as a disease, and to its successful treatment, is the current lack of biological markers that can be measured to accurately determine the relative states of impairment and health across the trajectory of SUDs. In addition, behavioral markers such as impulsivity, emotional regulation, and sensitivity to reward, may be used to predict response to treatment. NIDA will continue to support research to identify such biological and behavioral markers that predict treatment response as well as the likelihood that a person may relapse. Reliable metrics will enable providers to more accurately predict risk for and diagnose a SUD, predict which therapeutic intervention may be most effective, and intervene early in people at risk for relapse. Identification of mechanistic biomarkers of SUD risk will also serve to illuminate targets and pathways for medication development, as well as track treatment response to allow for faster testing and validation of medications and other interventions.

Approaches

- Correlate findings from 'omics studies (i.e. genomics, epigenomics, proteomics, metabolomics) to elucidate pathways and target proteins or molecules that may be linked with the biological mechanisms of SUDs at specific stages.
- Develop and test mobile sensing strategies as biomarkers for drug taking, recovery, and relapse risk.

Objective 3.4: Develop and test strategies for effectively and sustainably implementing evidence-based treatments

Validated treatment strategies for SUDs have great potential to make a positive impact on public health. The size of this impact, however, is limited by the inconsistent use of evidence-based interventions in real-world settings—an "evidence-to-practice gap." A 2012 NIDA workgroup report outlined deficiencies

in delivery of evidence-based treatments in SUD treatment centers, which included lack of medication-assisted treatment, recovery services, mental health assessments, and testing for infectious diseases (HIV, HCV, etc.), as well as lack of fidelity to evidence based practices in delivery of psychosocial interventions, among others[88].

Research is needed to identify specific barriers to, and facilitators of, implementation and to explore approaches to facilitating sustainable implementation of evidence-based practices—for example, research that addresses how various business practices, service-delivery models, coordinated care models, and screening and referral processes can improve treatment delivery and patient retention and outcomes. To address this need, NIDA will support research to develop and test strategies for effectively and sustainably implementing evidence-based treatments for SUDs in diverse healthcare delivery settings.

Approaches

- Identify the factors that influence effective dissemination and implementation of evidence-based practices for SUD treatment.
- Develop and validate novel implementation strategies for delivering evidence-based SUD treatment services in diverse healthcare settings.
- Develop and test innovative approaches to leverage technology to support implementation of evidence-based practices.

GOAL 4: Increase the public health impact of NIDA research and programs

Substance use, SUDs, and their consequences present a significant and ongoing public health burden in our nation. While it is important to support scientific research that will increase our understanding of the SUD disease processes and ultimately lead to better prevention and treatment options, it is also crucial to understand that there are many people in need of help right now. An estimated 7.1 million individuals in the U.S. are dependent on or abuse illicit drugs, yet only about 15% receive treatment[1].A range of public health issues are associated with the epidemic of opioid abuse, including opioid use disorders, opioid overdoses, neonatal abstinence syndrome, and increased spread of infectious diseases like HIV and hepatitis C (HCV)[7–10,83]. A number of other public health challenges are intertwined with these issues, including the significant unmet need for SUD treatment, changes in state policies related to marijuana, emerging drug trends including synthetic cannabinoids and cathinones, and the emergence of electronic cigarettes and vaporizers. Science can help to inform all of these issues and challenges.

Right now there are unprecedented opportunities for advancing SUD treatment across the nation. The combined effects of the Affordable Care Act (ACA) and requirements for parity of insurance coverage for behavioral health treatment are leading to a significant expansion in treatment access for SUDs and are creating financial incentives for integrating care for behavioral health disorders within the general healthcare system[89]. These changes, along with recent advances in addiction treatment, present a unique opportunity for advancing the SUD treatment field.

In addition, the rapid acceleration in the development and adoption of healthcare technologies—including electronic health records and mobile apps and sensors—has the potential to revolutionize healthcare as well as research. It will facilitate health information exchange, real-time patient monitoring and outreach, more efficient coordination of patient care, use of real-time analytics to drive a "learning healthcare system," new approaches for implementing evidence-based practices, use of biosensors to predict and intervene in advance of a relapse, and collation of large clinical data sets for pragmatic trials and population studies.

NIDA serves a number of roles relevant to public health, including supporting health services and epidemiology research, educating the public and relevant stakeholders on the science of drug use and addiction, helping to inform science-based decision making, and engaging in strategic partnerships to translate scientific advances into public health gains. Science can help to inform many important questions including:

- How can limited resources be most effectively used?
- How can prevention and treatment programs be better implemented?
- What impacts are various policies likely to have?
- How can we best leverage technology?
- How can we identify and intervene with vulnerable patients?
- Which healthcare models and payment systems promote the highest quality care?

[1] http://www.samhsa.gov/data/sites/default/files/National_BHBarometer_2014/National_BHBarometer_2014.pdf

To promote the use of science informed decision making to improve public health NIDA will:

- Determine the impact of drug use and addiction on families, peers, and society.
- Assess the impact of federal, state, and systems-level policies related to drug use and SUDs on public health and well-being.
- Increase strategic partnerships with the community to improve dissemination and implementation of evidence based research findings into policy and practice.

Objective 4.1: Determine the impact of drug use and addiction on families, peers, and society

The effects of drug use often go beyond the individual, affecting family, friends, and peers. Friends and family may experience significant stress due to financial impacts as well as concern for their loved one. Drug abuse also commonly affects the structure of a family because of divorce or the need to fill different roles to compensate for neglect of responsibilities by the drug user[52]. There is also an increased risk for interpersonal violence and child abuse and neglect (both physical and emotional), and these factors can lead to diminished attachments to parents and others, impaired self-regulation and problem solving, decreased development of prosocial attitudes and behaviors, and impairment of healthy development. In addition, parental drug use can have profound effects on children, from direct effects of using drugs while pregnant (e.g., neonatal abstinence syndrome) to impacts on perceptions of normative behaviors. Children of parents who abuse drugs have a greater risk for SUDs, depression, exposure to violence, and other health outcomes[90].

Drug abuse also has significant effects on society, including public health outcomes related to the spread of infectious diseases (HIV and HCV)[7,9]; public safety hazards like crime, violence, and drugged driving[53]; and a large economic burden associated with increased healthcare costs, lost work productivity, and criminal justice costs[2]. Understanding these consequences and the factors that influence their expression is critical for developing effective prevention, treatment, and mitigation strategies; for guiding development of laws and policies related to drug abuse; and for targeting limited resources to the efforts that will have the most potent effects.

Approaches

- Determine the impact of drug use and SUDs on public health outcomes.
- Clarify the impact of drug use and addiction on families and peers.
- Measure the societal costs associated with drug use and addiction.

Objective 4.2: Assess the impact of federal, state, and systems-level policies related to drug use and SUDs on public health and well-being

Diverse federal, state, and local laws and policies related to drug use and SUDs have the potential to affect public health and safety. This includes laws and policies that affect healthcare reimbursement, access to treatments, criminal sentencing, clean needle distribution, naloxone distribution, Good Samaritan laws, marijuana legalization for medical and or recreational purposes, drug testing, eligibility for social services, drugged driving, and alcohol and tobacco taxes. There is a significant need for research on these and other relevant policies to understand their effects on public health and safety, to

assess their cost-effectiveness, and to describe any unintended consequences to help inform future decision making.

Approaches

- Determine how laws and policies affect drug-use trends and prevalence of SUDs.
- Identify impacts on key health and social indicators, such as rates of use of other drugs, tobacco, and alcohol; rates of corollary risk and protective health behaviors; rates of transmitted infections including HIV and HCV; truancy, academic performance, and school dropout; crime and criminal justice outcomes; accidents associated with drugged driving; and employment outcomes.
- Track the impact of laws and policies on social norms, attitudes, beliefs, perceptions of harm and disapproval associated with drug use.
- Measure the economic impact of laws and policies including costs related to healthcare, criminal justice, and workplace productivity.

Objective 4.3: Increase strategic partnerships with the community to improve dissemination and implementation of evidence-based research findings into policy and practice

As discussed in Goals 2 and 3, there is a significant research-to-practice gap in the implementation of evidence-based prevention and treatment strategies. Implementation science develops and tests strategies for increasing effective and sustainable uptake of scientific advances by service and treatment providers, and these findings need to be applied in real-world settings. To accomplish this, strong partnerships with organizations that have the power to effect real-world implementation are needed.

Healthcare providers, payers, federal and state agencies, State Medicaid directors, public health agencies, educators, community coalitions, and others need to be engaged early and often throughout the development and testing of prevention and treatment interventions to ensure that real-world barriers (e.g., workforce, billing) are taken into consideration. These collaborations should also help researchers prioritize efforts to address critical ongoing barriers to effective prevention and treatment of SUDs.

Approaches

- Support the development of models to scale up evidence-based prevention and treatment interventions and implementation strategies.
- Explore non-traditional methods for addressing current barriers to effective prevention and treatment, such as workforce shortages and engagement of non-treatment seekers.
- Develop educational materials and training tools, including clinical decision support, to support effective dissemination of evidence-based practices
- Develop new methods for assessing service delivery outcomes of care in diverse settings in real time.

Priority Focus Areas

The four main goals listed above outline the broad scope of NIDA's strategic objectives over the next five years. Across these goals and objectives five priority focus areas have been identified that present unique opportunities to leverage over that time frame. These areas include:

1. Understanding the complex interactions of factors influencing drug use trajectories
2. Accelerating development of treatments
3. Addressing real world complexities
4. Advancing bi-directional translation
5. Building a strong, diverse, multi-disciplinary scientific workforce

1. Understanding the complex factors that influence drug-use trajectories

Behaviors such as drug use and addiction are mediated by numerous biological, environmental, social and developmental factors. Understanding the interactions among these factors and how they contribute to the risk for addiction and other negative consequences of drug use is critical for developing better prevention and treatment strategies. Basic and clinical addiction research have made significant progress in the identification of discrete genetic, epigenetic, neuro-circuitry, and behavioral factors that contribute to substance use disorders (SUDs)[37]. Moving forward, the integration of knowledge across scales and domains related to the complex expression of phenotypes will allow for a deeper and more clinically meaningful understanding of addiction which in turn can translate into better prevention and treatment interventions.

Advances in informatics and information technology (IT) are enabling more sophisticated types of analyses than ever before. Effectively leveraging these advances will require coordinated efforts including:

- Infrastructure development
- Multidisciplinary workforce training
- Culture change related to data sharing
- Consensus-based data standardization
- Support for large-scale data collection

NIDA recognizes that to achieve real progress toward understanding the human brain and how it is affected by drugs it is vital to develop more powerful analytical methods and visualization tools that can help capture the richness of data being generated from genetic, epigenetic, proteomic, metabolomic, brain-imaging, behavioral, clinical, social, and environmental studies. Neuroscience is fast approaching a data analysis bottleneck[91]. Dramatic advances in sequencing technologies, for example, have reached the point where it is now far cheaper to sequence whole genomes than to analyze the results. As a result, we are taking advantage of smaller and smaller fractions of the high density of data derived from various methodologies. A long-term effort is needed to develop the infrastructure necessary to analyze complex systems (drawing from mathematics, statistics, engineering, computer science and bioinformatics) in ways that allow researchers to investigate behaviors of non-linear, highly interacting systems. Such analytical and modeling tools are urgently required to take full advantage of the emerging

data sets and to address multi-faceted questions, such as how genes linked to addiction influence brain function and the response to drugs of abuse; how orchestrated genetic networks drive complex, adaptive brain function; and how social and environmental stimuli can interact with those networks to perturb their balance.

Over the next five years, NIDA will capitalize on emerging technologies and discoveries to facilitate integration and analysis of diverse data sources, including genomic, epigenomic, behavioral, neurobiological, environmental, and other phenotypic data associated with the stages of drug abuse and addiction. These efforts will focus on developing data sets and tools with the power to reveal hidden associations across organizational, temporal, and spatial scales and yield critical insights about brain function and development, genetic influence on brain and behavior development, and the biological precursors to and correlates of SUDs. These efforts will include:

The Adolescent Brain Cognitive Development (ABCD) Study. This landmark 10-year study led by NIDA in partnership with NIAAA, NCI, and other NIH partners (the Collaborative Research on Addiction at NIH, or CRAN) will establish a national, multisite, longitudinal cohort to prospectively examine the neurodevelopmental and behavioral effects of substance use from early adolescence (approximately age 9-10) until early adulthood, the period of highest risk for substance use and SUDs. This study will capture a broad range of data types, including measures of the impact of substance use (including alcohol, nicotine, marijuana, and illicit drugs) on physical health and development, psychosocial development, cognition (e.g., information processing, learning, memory, decision making), academic achievement, motivation, emotional regulation, and other behaviors and outcomes. In addition, data will be collected related to prenatal exposure, genetic, epigenetic, neurobiological, demographic, psychosocial, familial, and ecological factors that may influence the trajectory of substance use and its consequences. A single data analysis and informatics center will coordinate, standardize, and integrate all core data-collection, processing, storage, and analytic activities of the initiative.

The Addictome Project. This initiative will work to integrate diverse data types to enable meaningful analyses, assimilating a diverse, interoperable collection of multi-scale data sets that can be mined by the scientific community and visualized in a user-friendly framework to support discovery of novel relationships and scientific knowledge related to addiction. The Addictome will be a collection of numerous data types from diverse sources representing internal and external factors that contribute to an individual's risk for addiction across the lifespan. It will provide the infrastructure tools necessary to enable investigation into how these diverse factors interact within and across individuals to influence addiction risk and lead to diverse substance use trajectories. This project will be aligned with the Trans-NIH Big Data to Knowledge (BD2K) initiative.

It is also critical to ensure that, once created, these databases are effectively used. As a part of this effort, NIDA will work to:

- Develop standard data formats and common data elements for a user-friendly framework

- Ensure that addiction scientists are trained in the statistical and analytical methods needed to analyze these datasets.
- Provide incentives for contributing data to this initiative.
- Increase support for secondary data analyses.

Gene x Environment x Development Interplay (GxExD) Research. How environmental exposure impacts genetic and epigenetic factors to influence the risk for developing SUDs across development is critical for creating and improving prevention and treatment strategies- especially for SUDs for which there are few or no effective therapeutic interventions available. The primary challenge of GxExD research is to determine how small genetic effects across many genes combine to contribute to the overall risk for SUDs and how these genetic effects change with varying environmental exposures across human development.

A number of single gene variants that contribute to SUD risk have been identified. In addition, research has successfully identified some environmental contributors to risk. For example, when a person experiences extreme or prolonged stress, changes in their epigenetic profile can make him or her more susceptible to drug taking and addiction[92]. The nearly infinite biological complexity associated with individual genetics, variation in environmental exposures, and diversity in human behavioral responses make GxExD research particularly challenging. However, new advances in genetic and epigenetic technology coupled with increasing and evolving computational power are allowing such challenges to become increasingly tractable. Using these technologies to study complex GxExD interactions has the power to transform our fundamental understanding of how drug use and addiction evolve.

2. Accelerating development of treatments

The SUD treatment field has seen some important successes but significant challenges remain. There are currently three medications approved by the FDA to treat opioid addiction: buprenorphine, methadone, and extended release naltrexone[72]. While these have represented meaningful advances in the ability to treat opioid use disorders, the efficacy of these medications is far from ideal. In addition, while there are evidence based psychosocial treatments (e.g., cognitive-behavioral therapy, contingency management interventions, etc.) available for the treatment of cocaine, methamphetamine, or cannabis use disorders there are no approved medications for these SUDs. Moreover, many larger pharmaceutical companies are reticent to enter the addiction market due to the perception of a small market size, the difficulties in executing clinical trials in patients with SUDs (who frequently suffer from multiple comorbidities and who are often unlikely to adhere to the treatment protocol), and the high regulatory bar required to obtain approval by the FDA (i.e., the required focus on abstinence instead of harm reduction)[80].

To accelerate development of new medications for SUDs, NIDA supports a dual strategy. The first is a "repurposing" strategy that focuses on medications already approved for other indications that may also show potential benefit for treating (or preventing) SUDs. This approach aims to leverage existing safety profiles and pharmacology data to lower development costs and shorten the timeline for obtaining FDA approval. The second approach is to translate basic knowledge of the molecular pathways and brain

circuits involved in SUDs to develop new approaches that modulate specific targets and networks. In this context, novel therapeutic approaches include pharmacotherapies as well as biologics (e.g., vaccines, peptides) and non-pharmacological interventions such as transcranial magnetic stimulation, deep brain stimulation, and neurofeedback, which modify the activity of specific brain regions—and thus, may have fewer adverse effects.

NIDA will continue to prioritize efforts to de-risk drug development and foster strategic partnerships to accelerate the development of pharmaceuticals for SUDs using the combined strengths and resources of NIDA and outside organizations, including academic institutions, pharmaceutical and biotechnology companies, private and public foundations, and small businesses. In addition, efforts will focus on defining alternative end points other than abstinence – such as decreased drug use - that can be linked to improved patient outcomes to reduce the regulatory bar to obtain approval of new therapeutics. For example, a recent publication found that reduced use of cocaine decreased endothelial dysfunction, a marker of heart-disease risk that is characteristic of chronic cocaine use[93].

3. Addressing real-world complexities

The specific symptoms experienced by people with SUDs are shaped by complex, interacting factors that range from co-occurring physical and behavioral health conditions to social and environmental influences. In addition, while much of the research focuses on the effects of taking a single drug, we know that most drug use and SUDs involve poly-drug use. Further, different stages of life, such as adolescence, pregnancy, and old age confer unique risk factors and treatment needs. And finally, when effective, evidence based prevention and treatment strategies are developed there is often a significant research to practice gap in the implementation of these interventions. A broadening of research focus is necessary to include the context of such interacting complexities to develop and effectively disseminate interventions that meet the diverse needs associated with this variability in substance-use-related phenotypes.

Substance use and SUDs frequently occur in patients with psychiatric and physical health comorbidities. These conditions can often arise from shared causal factors, and these comorbidities can interact to affect symptom profiles, illness trajectory, and treatment outcomes[56,94]. As the field moves toward an integrative view of SUD, phenotypes should be defined in a way that captures these underlying causes. Rather than considering all SUDs together, varied SUD phenotypes should be separated based on functional domains that can be defined biologically. Indeed, defining the pathway from gene variation to molecular profile to neuron function and brain circuit activity and then to disordered behavior will enable a deeper understanding of addiction and reveal new targets for prevention and intervention.

The severity of any co-occurring condition can influence the course of another, which highlights the importance of effective integrated treatments. Along with psychiatric disorders, viral infections such as HIV and HCV frequently occur along with SUDs. In addition, SUDs are associated with increased risk of physical health comorbidities, including HIV, chronic pain conditions, and cardiovascular disease[95]. Recent healthcare reform efforts are prioritizing integrated medical care for people with SUDs, and more research is needed to inform the development of treatment delivery strategies that simultaneously address SUDs and co-occurring conditions.

The complexity of interacting biological, environmental, and social factors that contribute to and sustain SUDs presents significant opportunities for the application of precision medicine. An individual's environment, experience, and biology of an individual combines to determine their risk for developing an SUD, the trajectory the SUD will take, and the interventions that will be most effective for treating it. This is the inspiration behind the President's Precision Medicine Initiative, which will provide a foundation for the development of personalized interventions addressing the multiplicity of individual phenotypes.

More focused research is also needed to help address the significant research to practice gap in the implementation of evidence based prevention and treatment interventions. Closing the gap between research discovery and clinical and community practice is both a complex challenge and an absolute necessity if we are to ensure that all populations benefit from the Nation's investments in scientific discoveries. Research is needed to better understand the barriers to successful and sustainable implementation of evidence based practices and to develop implementation strategies that effectively overcome these barriers. Conversely, there is also a need for research that addresses how to reduce the use of strategies and procedures that are not evidence-based that may be harmful or wasteful.

NIDA will prioritize research that focuses on addressing real-world complexities. Efforts will focus on:

- Understanding the common underlying substrates and biological mechanisms that contribute to common comorbidities
- Research that incorporates real-world complexities including common comorbidities, pregnancy, development and aging, environmental stress, poly-substance use, etc.
- Development of prevention and treatment interventions that account for individual differences in biological, environmental, and social factors that impact SUD trajectories and phenotypes (precision medicine)
- Development and use of animal models that address real-world complexities
- Strategies to improve the effective and sustainable implementation of evidence based prevention and treatment interventions (implementation science)

4. Advancing Bi-Directional Translation

One core component of NIDA's mission is supporting research that will ultimately improve individual and public health. To support this goal, NIDA is fostering a strong bi-directional translational pipeline spanning basic neuroscience to clinical and applied research that is focused on the neurobiological substrates of addiction. Efforts are focused on integrating and coordinating human and animal research spanning all stages of drug use (i.e., initiation through recovery) and stages of development (i.e., from childhood through senescence), and across scales (i.e., molecular to societal).

Basic research should identify potential mechanisms and processes that may provide targets for intervention, - including new molecular, brain circuit, and behavioral targets - which should then rapidly be tested in humans. Clinical research findings should be translated in applied, patient-oriented and population-based research to facilitate broad implementation of best practices and improve public

health. Importantly insights from clinical and applied research should be modeled in basic research to identify and understand the underlying biological mechanisms involved.

Human and animal studies that use directly comparable outcome measures and testing conditions offer a powerful translational opportunity. A key integrative interface between clinical and basic studies is provided by human laboratory studies, including those with healthy volunteers. A recent reorganization of NIDA's Divisions and Branches was undertaken to foster bidirectional communication and interaction between clinical, applied and basic research efforts. NIDA's ongoing efforts in this area will promote strong collaborations across basic and clinical researchers to advance this goal.

5. Building a Strong, Diverse, Multi-Disciplinary Scientific Workforce

The entire biomedical research enterprise relies on the creativity, innovation, and dedication of the nation's scientific workforce. NIH and NIDA are committed to supporting a sustainable and robust workforce equipped to address the greatest challenges and opportunities in biomedical research.

NIDA recognizes that training and actively recruiting a truly diverse and multi-disciplinary workforce is a key to achieving our overall mission, and we will continue our commitment to attracting and training new investigators with diverse experiences and backgrounds. Efforts will focus on crafting new initiatives and enhancing traditional ones, such as the Diversity Supplements that are available for minority college students, graduate students, postdoctoral fellows, and investigator level scientists. In addition, NIDA is committed to addressing the full continuum of the training pipeline by continuing to support the long standing NIDA Summer Research Training Program for high school and college students, as well as providing grant-writing and research-proposal-development workshops for early-stage investigators.

NIDA also promotes opportunities for quantitative scientists from fields such as mathematics, bioengineering, and physics to apply their knowledge to the study of drug abuse and addiction. Through cross-disciplinary training and a focus on emerging technologies and scientific opportunities, NIDA seeks to promote a cutting-edge research workforce that will advance the knowledge base needed to address these public health problems.

Attracting and retaining a well-trained cadre of clinicians, chemists, physicists, bioengineers, statisticians, mathematicians, and others who can conduct research on various aspects of addiction will foster a strong multidisciplinary workforce capable of addressing the challenges of addiction research. NIDA's efforts in this area will focus on:

- Increasing the number of scientists with multi-disciplinary training necessary to address the complexities of addiction research.
- Supporting the development of a high-quality, diverse, and sustainable scientific workforce
- Enhancing recruitment and mentoring of underrepresented investigators.
- Improving mentoring of young scientists.

Ensuring the effective translation, implementation, and dissemination of scientific research findings to improve the prevention and treatment of substance use disorders and enhance public awareness of addiction as a brain disease

Addiction science can only improve public health if research findings effectively reach the people who can benefit from them and if the public's understanding of drug abuse is changed by new knowledge. One of NIDA's central roles is to be the trusted source of data related to drug use and addiction and ensure that new findings are rapidly and effectively disseminated to the field and to the wider public.

A crucial aspect of this mandate is to promote wider recognition of addiction as a chronic relapsing brain disease. Addiction is a disease that powerfully compromises executive function circuits that mediate self-control and decision making; failure to understand this often results in stigma against people with SUDs. This stigma has contributed to the slow adoption of effective medical treatments for addiction, including medication assisted treatments for opioid use disorders such as methadone and buprenorphine[96]. It has also impeded implementation of evidence-based harm-reduction approaches like needle-exchange programs to prevent the spread of HIV and Hepatitis C[97]. Effective dissemination of research findings can facilitate evidence-based decision making and drive improvements in public health.

NIDA's communication efforts are targeted to a broad range of stakeholders, including healthcare providers, teens, parents, educators, community organizations, policymakers, and others. Our NIDAMED and Blending initiatives develop educational materials including continuing medical education (CME) courses to train healthcare providers on evidence-based practices and cover screening individuals for risky substance use, prescribing for pain, and treating adolescents with SUDs.

NIDA strives to make addiction research more accessible to people in the community by strategically leveraging social media, blogs, and the news media to promote new findings, inform the public about emerging drug trends, and educate the community on addiction science. NIDA also engages in various forms of outreach targeted to adolescents, including our popular teen-oriented Drugs and Health blog, our annual Drug Facts Week events that engage participating schools across the country, and Drug Facts Chat Day, in which NIDA scientists answer questions from middle and high school students in an all-day, real-time virtual chat.

While adolescents are at the greatest risk for drug use, it can be difficult to reach this audience directly; therefore NIDA works to educate various teen influencers including parents, teachers, and the media. NIDA produces materials aimed at helping parents and teachers communicate with children and teens about drugs, such as web-based FAQs and our Family Checkup tool.

Approaches

- Use evidence-based communication strategies to disseminate relevant findings from scientific research to all stakeholders.

- Provide clear, comprehensive, and up-to-date scientific information to guide policy making related to drug use and related disorders.

HIGHLIGHTS

The final draft will incorporate short highlights on a number of NIDA programs including:

- The Adolescent Brain Cognitive Development (ABCD) Study
- Big Data Initiatives
- Mobile Health
- Methamphetamine Monoclonal Antibody (ch-mAb7F9) Development
- Clinical Decision Support for Opioid Use Disorders
- JJ-Trials
- Miniature Microscope for Deep Brain Imaging in Animals
- Avenir Awards
- Research on Women and Sex Differences
- The Pharmacogenomics of Pain
- HIV Reservoirs
- Transcranial Magnetic Stimulation
- Neuroscience Technologies
- Intranasal Naloxone
- NIDAMED
- The Neuroscience of Addiction
- Epigenetics

Trans-NIH Initiatives

Collaborative Research on Addiction at NIH (CRAN)

The mission of the National Institutes of Health (NIH) partnership, Collaborative Research on Addiction at NIH (CRAN), is to provide a strong collaborative framework to enable the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Cancer Institute (NCI) to integrate resources and expertise to advance substance use, abuse, and addiction research and public health outcomes.

HIV/AIDS Research at NIH

The Office of AIDS Research coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. Through its annual comprehensive trans-NIH planning, budgeting, and portfolio-assessment processes, OAR sets scientific priorities, enhances collaboration, and ensures that research dollars are invested in the highest priority areas of scientific opportunity that will lead to new tools in the global fight against AIDS. New strategic priorities were announced in August 2015 that will guide NIH and NIDA funding related to HIV and AIDS research.

NIH Blueprint for Neuroscience Research

The NIH Blueprint is a collaborative framework that includes the NIH Office of the Director and the 15 NIH Institutes (including NIDA) and Centers that support research on the nervous system. By pooling resources and expertise, the Blueprint identifies cross-cutting areas of research and confronts

challenges too large for any single Institute or Center. NIDA plays a leading role in a number of NIH Blueprint projects that contribute to our strategic goals and objectives:

A. The **Human Connectome Project,** an effort to map the connections within the healthy brain, is expected to help answer questions about how genes influence brain connectivity and how this, in turn, relates to mood, personality, and behavior. The investigators will collect brain-imaging data plus genetic and behavioral data from 1,200 adults. They are working to optimize brain-imaging techniques to see the brain's wiring in unprecedented detail.
B. The **Blueprint Neurotherapeutics Network** is helping small labs develop new drugs for nervous system disorders. The Network provides research funding plus access to millions of dollars' worth of services and expertise to assist in every step of the drug-development process, from laboratory studies to preparation for clinical trials. Project teams across the U.S. have received funding to pursue drugs for conditions from vision loss to neurodegenerative disease to depression. NIDA is coordinating a smoking cessation project utilizing orexin receptor antagonists.
C. The **Neuroscience Information Framework (NIF),** which NIDA led the effort to establish, is an online portal to neuroscience information that includes a customized search engine, a curated registry of resources, and direct access to more than 100 online databases. NIF advances neuroscience research by enabling discovery and access to public research data and tools worldwide through an open-source, networked environment.
D. **Blueprint Training Initiatives**, for which NIDA has also taken a leadership role, provide support for undergraduate and graduate student research training in the areas of computational neuroscience and multimodal neuroimaging. These two programs were extended for another funding round, due to their demonstrated highly successful outcomes.

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative

The BRAIN initiative, launched by President Obama in 2013, is a coordinated effort among public and private organizations aimed at revolutionizing our understanding of the human brain. Significant breakthroughs in how we treat neurological and psychiatric disease will require a new generation of tools to enable researchers to investigate the functions of the brain in much greater detail and at faster speeds. This initiative will accelerate technology development at the intersections of nanoscience, imaging, engineering, informatics, and other rapidly emerging fields of science to achieve this goal.

NIH Big Data to Knowledge (BD2K) Initiative

BD2K is a trans-NIH initiative established to enable biomedical research as a digital research enterprise, to facilitate discovery and support new knowledge, and to maximize community engagement. The initiative is working to enhance the utility of biomedical Big Data by:

- Facilitating broad use of biomedical data by making them discoverable, accessible, and citable
- Conducting research to develop methods, software, and tools to analyze biomedical Big Data
- Enhancing training necessary for biomedical Big Data science
- Supporting a data ecosystem that accelerates discovery as part of a digital enterprise

The NIH Common Fund

The NIH Common Fund provides a strategic and nimble approach to address key roadblocks in biomedical research that impede basic scientific discovery and its translation into improved human health, and to capitalize on emerging opportunities to catalyze the rate of progress across multiple biomedical fields. The Common Fund supports 32 programs; NIDA plays key roles in:

A. **The NIH Common Fund Epigenomics Program:** This program is aimed at generating new research tools, technologies, and datasets to accelerate our understanding of how genome-wide chemical modifications to DNA and DNA-associated proteins regulate gene activity without altering the DNA sequence itself and what role these modifications play in health and disease.
B. **The 4D Nucleome (4DN) Program:** It is estimated that each human cell contains approximately 2 meters (6.5 feet) of DNA, squeezed inside the cell's microscopic nucleus in tightly controlled arrangement. This program aims to develop technologies, resources, and data to understand the principles underlying the organization of DNA in space and time, the role nuclear organization plays in gene expression and cellular function, and how changes in nuclear organization affect normal development as well as various diseases.
C. **The Genotype-Tissue Expression (GTEx) Program:** This program examines human gene expression and regulation in multiple tissues, providing valuable insights into the mechanisms of gene regulation. Genetic variation between individuals will be examined for correlation with differences in gene expression level to identify regions of the genome that influence if and how much a gene is expressed. These types of studies are important for determining the role that genetics plays along the SUD trajectory.
D. **The Druggable (IDG) Genome Program:** The goal of this program is to improve our understanding of the properties and functions of proteins that are commonly targeted for drug development: G-protein coupled receptors, nuclear receptors, ion channels, and protein kinases. The program is creating a data resource center that will catalog known information about these proteins to help identify and prioritize targets for further study, and it will develop the technologies necessary to elucidate their function.
E. **Extracellular RNA Communication Program (ERCP):** This program aims to discover fundamental biological principles about the mechanisms of extracellular ribonucleic acid (exRNA) generation, secretion, and transport; to identify and develop a catalog of exRNAs found in normal human body fluids; and to investigate the potential for using exRNAs in the clinic as therapeutic molecules or biomarkers of disease.

The NIH Pain Consortium

The NIH Pain Consortium was established to enhance pain research and promote collaboration among researchers across the many NIH Institutes and Centers that have programs and activities addressing pain. The Pain Consortium works to develop a comprehensive multi-disciplinary pain research agenda for the NIH and to increase visibility for pain research both within NIH and with external stakeholders.

Marijuana Research at NIH

Interest in the potential therapeutic effects marijuana and its constituents has been growing rapidly, partially in response to media attention surrounding the use of cannabidiol (CBD) in young children with

intractable seizure disorders[98]. To date, 23 states and the District of Columbia (DC) have legalized marijuana for medicinal use. While there is significant preliminary research supporting the potential therapeutic value of marijuana-derived compounds for a number of conditions, there is not yet sufficient evidence to support new drug approval. There is a pressing need for rigorous clinical research in this area.

As part of NIDA's mission, we support research on both the adverse effects of marijuana use and the potential therapeutic value of marijuana and its components for the treatment of substance use disorders and pain. Research on potential therapeutic potential for other health conditions is supported by other NIH institutes as it aligns with their mission. For example, the efficacy of marijuana-derived compounds, such as CBD, for the treatment of epilepsy is studied by the National Institute on Neurological Disorders and Stroke (NINDS), potential uses in cancer treatment are studied by National Cancer Institute (NCI), and so on. NIDA provides marijuana for research through the NIDA Drug Supply Program and will continue to coordinate with other NIH institutes and centers to support research in this area. For example, in 2015 NIDA partnered with six other NIH institutes to develop a program announcement on Developing the Therapeutic Potential of the Endocannabinoid System for Pain Treatment.

References

1. Substance Abuse and Mental Health Services Administration. Results from the 2014 National Survey on Drug Use and Health: Detailed Tables. (2015). at <http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.pdf>
2. U.S. Department of Justice National Drug Intelligence Center. National Drug Threat Assessment 2011. (2011). at <http://www.justice.gov/archive/ndic/pubs44/44849/44849p.pdf>
3. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. (2014). at <http://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf>
4. Volkow, N. D. & Baler, R. D. Addiction science: Uncovering neurobiological complexity. *Neuropharmacology* **76,** 235–249 (2014).
5. Jinek, M. *et al.* A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* **337,** 816–821 (2012).
6. *Health Information Technology for Economic and Clinical Health (HITECH) Act*. (2009). at <http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/hitechact.pdf>
7. Conrad, C. *et al.* Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone--Indiana, 2015. *MMWR Morb. Mortal. Wkly. Rep.* **64,** 443–444 (2015).
8. Wheeler, E., Jones, T. S., Gilbert, M. K. & Davidson, P. J. Opioid Overdose Prevention Programs Providing Naloxone to Laypersons - United States, 2014. *MMWR Morb. Mortal. Wkly. Rep.* **64,** 631–635 (2015).
9. Zibbell, J. E. *et al.* Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. *MMWR Morb. Mortal. Wkly. Rep.* **64,** 453–458 (2015).
10. Tolia, V. N. *et al.* Increasing Incidence of the Neonatal Abstinence Syndrome in U.S. Neonatal ICUs. *N. Engl. J. Med.* 150426153016002 (2015). doi:10.1056/NEJMsa1500439
11. Spoth, R. *et al.* Longitudinal effects of universal preventive intervention on prescription drug misuse: three randomized controlled trials with late adolescents and young adults. *Am. J. Public Health* **103,** 665–672 (2013).
12. Deyo, R. A. *et al.* Measures Such As Interstate Cooperation Would Improve The Efficacy Of Programs To Track Controlled Drug Prescriptions. *Health Aff. (Millwood)* **32,** 603–613 (2013).
13. Haegerich, T. M., Paulozzi, L. J., Manns, B. J. & Jones, C. M. What we know, and don't know, about the impact of state policy and systems-level interventions on prescription drug overdose. *Drug Alcohol Depend.* **145,** 34–47 (2014).
14. Franklin, G. *et al.* A Comprehensive Approach to Address the Prescription Opioid Epidemic in Washington State: Milestones and Lessons Learned. *Am. J. Public Health* **105,** 463–469 (2015).
15. Johnson, H. *et al.* Decline in drug overdose deaths after state policy changes - Florida, 2010-2012. *MMWR Morb. Mortal. Wkly. Rep.* **63,** 569–574 (2014).
16. Robinson, A. & Wermeling, D. P. Intranasal naloxone administration for treatment of opioid overdose. *Am. J. Health-Syst. Pharm. AJHP Off. J. Am. Soc. Health-Syst. Pharm.* **71,** 2129–2135 (2014).
17. Walley, A. Y. *et al.* Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* **346,** f174–f174 (2013).
18. Gifford, E. J., Eldred, L. M., McCutchan, S. A. & Sloan, F. A. The effects of participation level on recidivism: a study of drug treatment courts using propensity score matching. *Subst. Abuse Treat. Prev. Policy* **9,** 40 (2014).

19. Kakko, J., Svanborg, K. D., Kreek, M. J. & Heilig, M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *The Lancet* **361,** 662–668 (2003).
20. Schwartz, R. P. *et al.* Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009. *Am. J. Public Health* **103,** 917–922 (2013).
21. Johnson, R. E. *et al.* A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend.* **40,** 17–25 (1995).
22. Hartung, D. M. *et al.* Extended-release naltrexone for alcohol and opioid dependence: a meta-analysis of healthcare utilization studies. *J. Subst. Abuse Treat.* **47,** 113–121 (2014).
23. Havens, J. R., Leukefeld, C. G., DeVeaugh-Geiss, A. M., Coplan, P. & Chilcoat, H. D. The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers. *Drug Alcohol Depend.* **139,** 9–17 (2014).
24. Cicero, T. J., Ellis, M. S. & Surratt, H. L. Effect of abuse-deterrent formulation of OxyContin. *N. Engl. J. Med.* **367,** 187–189 (2012).
25. Meier, M. H. *et al.* Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc. Natl. Acad. Sci. U. S. A.* **109,** E2657–2664 (2012).
26. Knudsen, H. K., Abraham, A. J. & Oser, C. B. Barriers to the implementation of medication-assisted treatment for substance use disorders: the importance of funding policies and medical infrastructure. *Eval. Program Plann.* **34,** 375–381 (2011).
27. Weaver, M. F., Hopper, J. A. & Gunderson, E. W. Designer drugs 2015: assessment and management. *Addict. Sci. Clin. Pract.* **10,** 8 (2015).
28. Breland, A. B., Spindle, T., Weaver, M. & Eissenberg, T. Science and Electronic Cigarettes: Current Data, Future Needs. *J. Addict. Med.* **8,** 223–233 (2014).
29. Leventhal, A. M. *et al.* Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA* **314,** 700–707 (2015).
30. Indiana State Department of Health. HIV Outbreak in Southeastern Indiana. (2015). at <http://www.in.gov/isdh/26649.htm>
31. Centers for Disease Control and Prevention (CDC). HIV-associated behaviors among injecting-drug users--23 Cities, United States, May 2005-February 2006. *MMWR Morb. Mortal. Wkly. Rep.* **58,** 329–332 (2009).
32. Normand, J., Montaner, J., Fang, C.-T., Wu, Z. & Chen, Y.-M. HIV: Seek, test, treat, and retain. *J. Food Drug Anal.* **21,** S4–S6 (2013).
33. Malta, M., Strathdee, S. A., Magnanini, M. M. F. & Bastos, F. I. Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review. *Addict. Abingdon Engl.* **103,** 1242–1257 (2008).
34. Dolgin, E. Drug discoverers chart path to tackling data irreproducibility. *Nat. Rev. Drug Discov.* **13,** 875–876 (2014).
35. Prinz, F., Schlange, T. & Asadullah, K. Believe it or not: how much can we rely on published data on potential drug targets? *Nat. Rev. Drug Discov.* **10,** 712 (2011).
36. Collins, F. S. & Tabak, L. A. Policy: NIH plans to enhance reproducibility. *Nature* **505,** 612–613 (2014).
37. Shurtleff, D., Sasek, C. & Kautz, M. NIDA 40th Anniversary Issue. *Neuropharmacology* **76,** 195–600 (2014).
38. Ferguson, S. M. & Neumaier, J. F. Grateful DREADDs: Engineered Receptors Reveal How Neural Circuits Regulate Behavior. *Neuropsychopharmacology* **37,** 296–297 (2012).
39. Mahler, S. V. *et al.* Designer receptors show role for ventral pallidum input to ventral tegmental area in cocaine seeking. *Nat. Neurosci.* **17,** 577–585 (2014).
40. Genberg, B. L. *et al.* Trajectories of Injection Drug Use Over 20 Years (1988-2008) in Baltimore, Maryland. *Am. J. Epidemiol.* **173,** 829–836 (2011).

41. Kertesz, S. G. *et al.* Trajectories of Drug Use and Mortality Outcomes Among Adults Followed Over 18 Years. *J. Gen. Intern. Med.* **27,** 808–816 (2012).
42. Goldman, D., Oroszi, G. & Ducci, F. The genetics of addictions: uncovering the genes. *Nat. Rev. Genet.* **6,** 521–532 (2005).
43. Conroy, D. A. & Arnedt, J. T. Sleep and substance use disorders: an update. *Curr. Psychiatry Rep.* **16,** 487 (2014).
44. Chen, Y. & Kalichman, S. C. Synergistic effects of food insecurity and drug use on medication adherence among people living with HIV infection. *J. Behav. Med.* **38,** 397–406 (2015).
45. Murphy, A., Taylor, E. & Elliott, R. The detrimental effects of emotional process dysregulation on decision-making in substance dependence. *Front. Integr. Neurosci.* **6,** 101 (2012).
46. Bernstein, J. *et al.* The association of injury with substance use disorder among women of reproductive age: an opportunity to address a major contributor to recurrent preventable emergency department visits? *Acad. Emerg. Med. Off. J. Soc. Acad. Emerg. Med.* **21,** 1459–1468 (2014).
47. Vinson, D. C. Marijuana and other illicit drug use and the risk of injury: A case-control study. *Mo. Med.* **103,** 152–156 (2006).
48. Choo, E. K. *et al.* The intersecting roles of violence, gender, and substance use in the emergency department: a research agenda. *Acad. Emerg. Med. Off. J. Soc. Acad. Emerg. Med.* **21,** 1447–1452 (2014).
49. Pickard, H. & Fazel, S. Substance abuse as a risk factor for violence in mental illness: some implications for forensic psychiatric practice and clinical ethics. *Curr. Opin. Psychiatry* 1 (2013). doi:10.1097/YCO.0b013e328361e798
50. King, K. M., Meehan, B. T., Trim, R. S. & Chassin, L. Marker or mediator? The effects of adolescent substance use on young adult educational attainment. *Addiction* **101,** 1730–1740 (2006).
51. Aubry, T., Klodawsky, F. & Coulombe, D. Comparing the housing trajectories of different classes within a diverse homeless population. *Am. J. Community Psychol.* **49,** 142–155 (2012).
52. Center for Substance Abuse Treatment. *Substance Abuse Treatment and Family Therapy*. (Substance Abuse and Mental Health Services Administration (US), 2004). at <http://www.ncbi.nlm.nih.gov/books/NBK64265/>
53. Bureau of Justice Statistics, Office of Justice Programs, U.S. Department of Justice. Drugs and Crime Facts. at <http://www.bjs.gov/content/dcf/duc.cfm>
54. Henkel, D. Unemployment and substance use: a review of the literature (1990-2010). *Curr. Drug Abuse Rev.* **4,** 4–27 (2011).
55. Littlejohn, C., Bannister, J. & Baldacchino, A. Comorbid chronic non-cancer pain and opioid use disorders. *Hosp. Med. Lond. Engl. 1998* **65,** 210–214 (2004).
56. Grant, B. F. *et al.* Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch. Gen. Psychiatry* **61,** 807–816 (2004).
57. Faggiano, F., Minozzi, S., Versino, E. & Buscemi, D. Universal school-based prevention for illicit drug use. *Cochrane Database Syst. Rev.* **12,** CD003020 (2014).
58. Spoth, R., Trudeau, L., Shin, C. & Redmond, C. Long-term effects of universal preventive interventions on prescription drug misuse. *Addict. Abingdon Engl.* **103,** 1160–1168 (2008).
59. Acion, L., Ramirez, M. R., Jorge, R. E. & Arndt, S. Increased risk of alcohol and drug use among children from deployed military families: Substance use among military children. *Addiction* **108,** 1418–1425 (2013).
60. Vassoler, F. M., Byrnes, E. M. & Pierce, R. C. The impact of exposure to addictive drugs on future generations: Physiological and behavioral effects. *Neuropharmacology* **76,** 269–275 (2014).

61. Yohn, N. L., Bartolomei, M. S. & Blendy, J. A. Multigenerational and transgenerational inheritance of drug exposure: The effects of alcohol, opiates, cocaine, marijuana, and nicotine. *Prog. Biophys. Mol. Biol.* **118,** 21–33 (2015).
62. Marschall-Lévesque, S., Castellanos-Ryan, N., Vitaro, F. & Séguin, J. R. Moderators of the association between peer and target adolescent substance use. *Addict. Behav.* **39,** 48–70 (2014).
63. Leve, L. D., Fisher, P. A. & Chamberlain, P. Multidimensional Treatment Foster Care as a Preventive Intervention to Promote Resiliency Among Youth in the Child Welfare System. *J. Pers.* **77,** 1869–1902 (2009).
64. Bruce, J., Fisher, P. A., Pears, K. C. & Levine, S. Morning cortisol Levels in preschool-aged foster children: differential effects of maltreatment type. *Dev. Psychobiol.* **51,** 14–23 (2009).
65. Johnston, L. D., O'Malley, P. M., Miech, R. A., Bachman, J. G. & Schulenberg, J. E. Monitoring the Future national survey results on drug use: 1975-2014: Overview, key findings on adolescent drug use. (2015). at <http://www.monitoringthefuture.org//pubs/monographs/mtf-overview2014.pdf>
66. Tschann, J. M. *et al.* Initiation of substance use in early adolescence: the roles of pubertal timing and emotional distress. *Health Psychol. Off. J. Div. Health Psychol. Am. Psychol. Assoc.* **13,** 326–333 (1994).
67. Sinha, R. Chronic Stress, Drug Use, and Vulnerability to Addiction. *Ann. N. Y. Acad. Sci.* **1141,** 105–130 (2008).
68. Bachman, J. G. *Smoking, drinking, and drug use in young adulthood: the impacts of new freedoms and new responsibilities*. (L. Erlbaum Associates, 1997).
69. Burdzovic Andreas, J. & Jackson, K. M. Adolescent Alcohol Use Before and After the High School Transition. *Alcohol. Clin. Exp. Res.* **39,** 1034–1041 (2015).
70. Dusenbury, L. A review of research on fidelity of implementation: implications for drug abuse prevention in school settings. *Health Educ. Res.* **18,** 237–256 (2003).
71. Keyes, K. M. *et al.* Childhood maltreatment and the structure of common psychiatric disorders. *Br. J. Psychiatry* **200,** 107–115 (2012).
72. Mann, C., Frieden, T., Hyde, P. S., Volkow, N. D. & Koob, G. F. Informational Bulletin : Medication Assisted Treatment for Substance Use Disorders. (2014). at <http://www.samhsa.gov/sites/default/files/topics/behavioral_health/medication-assisted-treatment-joint-bulletin.pdf>
73. Carroll, K. M. & Onken, L. S. Behavioral Therapies for Drug Abuse. *Am. J. Psychiatry* **162,** 1452–1460 (2005).
74. McLellan, A. T., Lewis, D. C., O'Brien, C. P. & Kleber, H. D. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* **284,** 1689–1695 (2000).
75. Montoya, I. D. Advances in the development of biologics to treat drug addictions and overdose. *Adicciones* **24,** 95–103 (2012).
76. Montoya, I. D. & Vocci, F. Novel medications to treat addictive disorders. *Curr. Psychiatry Rep.* **10,** 392–398 (2008).
77. Sokhadze, T. M., Cannon, R. L. & Trudeau, D. L. EEG biofeedback as a treatment for substance use disorders: review, rating of efficacy, and recommendations for further research. *Appl. Psychophysiol. Biofeedback* **33,** 1–28 (2008).
78. Kravitz, A. V. *et al.* Cortico-striatal circuits: Novel therapeutic targets for substance use disorders. *Brain Res.* (2015). doi:10.1016/j.brainres.2015.03.048
79. Gonzales, R., Ang, A., Murphy, D. A., Glik, D. C. & Anglin, M. D. Substance use recovery outcomes among a cohort of youth participating in a mobile-based texting aftercare pilot program. *J. Subst. Abuse Treat.* **47,** 20–26 (2014).
80. Willyard, C. Pharmacotherapy: Quest for the quitting pill. *Nature* **522,** S53–S55 (2015).

81. Petterson, S. M. *et al.* Why there must be room for mental health in the medical home. *Am. Fam. Physician* **77,** 757 (2008).
82. *Improving Patient Treatment Adherence*. (Springer New York, 2010). at <http://link.springer.com/10.1007/978-1-4419-5866-2>
83. Volkow, N. D., Frieden, T. R., Hyde, P. S. & Cha, S. S. Medication-Assisted Therapies — Tackling the Opioid-Overdose Epidemic. *N. Engl. J. Med.* **370,** 2063–2066 (2014).
84. Agrawal, A. *et al.* The genetics of addiction-a translational perspective. *Transl. Psychiatry* **2,** e140 (2012).
85. Nielsen, D. A., Nielsen, E. M., Dasari, T. & Spellicy, C. J. Pharmacogenetics of addiction therapy. *Methods Mol. Biol. Clifton NJ* **1175,** 589–624 (2014).
86. Institute of Medicine (US) Committee on Crossing the Quality Chasm: Adaptation to Mental Health and Addictive Disorders. *Improving the Quality of Health Care for Mental and Substance-Use Conditions: Quality Chasm Series*. (National Academies Press (US), 2006). at <http://www.ncbi.nlm.nih.gov/books/NBK19830/>
87. McCann, D. J., Ramey, T. & Skolnick, P. Outcome Measures in Medication Trials for Substance Use Disorders. *Curr. Treat. Options Psychiatry* (2015). doi:10.1007/s40501-015-0041-x
88. National Advisory Council on Drug Abuse Workgroup. Adoption of NIDA's Evidence-Based Treatments in Real World Settings. (2012). at <https://www.drugabuse.gov/sites/default/files/files/evidence-based_treatments_in_real_world_settings_workgroup_report.pdf>
89. Wen, H., Cummings, J. R., Hockenberry, J. M., Gaydos, L. M. & Druss, B. G. State Parity Laws and Access to Treatment for Substance Use Disorder in the United States: Implications for Federal Parity Legislation. *JAMA Psychiatry* **70,** 1355 (2013).
90. *Impact of substance abuse on children and families: research and practice implications*. (Haworth Press, Inc, 2006).
91. Worthey, E. A. in *Current Protocols in Human Genetics* (eds. Haines, J. L. et al.) 9.24.1–9.24.24 (John Wiley & Sons, Inc., 2013). at <http://doi.wiley.com/10.1002/0471142905.hg0924s79>
92. Pizzimenti, C. L. & Lattal, K. M. Epigenetics and memory: causes, consequences and treatments for post-traumatic stress disorder and addiction. *Genes Brain Behav.* **14,** 73–84 (2015).
93. Lai, H. *et al.* Cocaine Abstinence and Reduced Use Associated With Lowered Marker of Endothelial Dysfunction in African Americans: A Preliminary Study. *J. Addict. Med.* **9,** 331–339 (2015).
94. Herbeck, D. M. *et al.* Treatment Compliance in Patients with Comorbid Psychiatric and Substance Use Disorders. *Am. J. Addict.* **14,** 195–207 (2005).
95. National Institute on Drug Abuse. Medical Consequences of Drug Abuse. at <http://www.drugabuse.gov/related-topics/medical-consequences-drug-abuse>
96. Rieckmann, T., Kovas, A. E. & Rutkowski, B. A. Adoption of medications in substance abuse treatment: priorities and strategies of single state authorities. *J. Psychoactive Drugs* **Suppl 6,** 227–238 (2010).
97. Rich, J. D. & Adashi, E. Y. Ideological Anachronism Involving Needle and Syringe Exchange Programs: Lessons From the Indiana HIV Outbreak. *JAMA* **314,** 23 (2015).
98. Cilio, M. R., Thiele, E. A. & Devinsky, O. The case for assessing cannabidiol in epilepsy. *Epilepsia* **55,** 787–790 (2014).